THE INFLUENCE OF FOOD INGESTION UPON ENDogenous PURINE METABOLISM. I.

BY WILLIAM C. ROSE.

(From the Laboratory of Biological Chemistry, School of Medicine, University of Texas, Galveston.)

(Received for publication, August 24, 1921.)

Abundant evidence has been accumulated in recent years to indicate that the original idea of Burian and Schur (1) and Siven (2), to the effect that the excretion of endogenous purines is constant from day to day in the same individual, is not correct. More than 15 years ago Folin (3) found that the change from a diet of milk and eggs to one of starch and cream might be accompanied by a fall in uric acid elimination of practically 50 per cent, although both diets are purine-free. He stated that the uric acid excretion is reduced whenever the total nitrogen elimination is much diminished, but that the reduction is irregular, and variable for different individuals.

Since the work of Folin, numerous investigators, notably Leathes (4), Mendel and Brown (5), Smetánka (6), Taylor and Rose (7), Mendel and Stehle (8), Lewis and Doisy (9), and Höst (10), have corroborated his findings that protein ingestion exerts a marked influence upon urinary uric acid. Smetánka (6), Mendel and Stehle (8), and Umeda (11) also observed an increase in uric acid elimination, as compared with the fasting output, following the ingestion of carbohydrates. Apparently fats produce the least effect upon purine metabolism of either of the three food-stuffs.

The calorific value of the diet is likewise important in determining the uric acid excretion. According to Graham and Poulton (12), diets of protein and fat of insufficient calorie value, cause a fall of 30 to 50 per cent in the output of endogenous uric acid. If most of the fat is replaced by carbohydrate no fall is observed. More recently Höst (10) has affirmed that every increase or
decrease in the calorific value of the food beyond a certain minimum, is accompanied by a like change in uric acid excretion. This effect occurs no matter which foodstuff is responsible for the variation in energy value of the diet, but is greatest with changes due to protein.

No unanimity of opinion exists, however, as to the cause of the increases and decreases in endogenous uric acid elimination induced by diet. Various factors have been held responsible, and at least six possible explanations have been suggested or advocated in an effort to explain the experimental observations. It is our purpose in this paper to briefly discuss these theories. In the succeeding communication data will be presented which we believe throw additional light on the problem.

Alterations in the excretion of endogenous uric acid resulting from variations in the kind and amount of food have been attributed to the following factors: (1) Nuclear disintegration in the glands of the alimentary canal occasioned by the work of digestion (Mareš (13), Smetánka (6), Lambling and Dubois (14), Mendel and Stehle (8), Høst (10)). (2) Nuclear disintegration associated with the work of digestion and food storage (Smetánka, 6). (3) Synthesis of purines from carbohydrates (Graham and Poulton (12), Umeda (11)). (4) Synthesis of purines from arginine and histidine (Ackroyd and Hopkins (15), Harding and Young (16)). (5) Stimulation of the process of elimination (suggested by Lewis, Dunn, and Doisy (17), but regarded by them as untenable). (6) General stimulation of cellular metabolism by amino-acids or their catabolic derivatives (Lewis, Dunn, and Doisy, 17).

The first of these theories was suggested by Mareš (13). This investigator attributed the increase in output of uric acid following the consumption of purine-free food to nuclear disintegration, chiefly in the alimentary glands, incidental to the physiological work of secretion and digestion. Uric acid thus represents, according to Mareš, the wear and tear of these glandular tissues. When the alimentary glands are resting, the output of uric acid is low; when they are actively synthesizing and secreting digestive fluids, wear and tear is increased, and the production of uric acid is accelerated. As further evidence for this mechanism, Mareš points to the fact that pilocarpine, which is known to increase secretory activity, likewise augments the excretion of uric acid.
Smetánka (6), Lambing and Dubois (14), and Höst (10) also regard digestive work as an important factor in the variations in output of endogenous uric acid. Mendel and Stehle (8), on the other hand, state that their experiments "offer no obstacle to the assumption that a portion, at least, of the endogenous uric acid may originate from the activity of the alimentary secretory apparatus." The latter investigators were able to confirm the findings of Mareš in regard to the action of pilocarpine, and to make the additional observation that atropine, which diminishes secretory activity, causes a fall in uric acid elimination.

The Mareš theory seems inadequate to us for several reasons. It does not appear probable that disintegration of the secretory cells during the process of digestion would be sufficiently extensive to account for the increase in uric acid elimination, which in some case is relatively large (cf. Taylor and Rose (7)). It is true that the suggestion of Mendel and Stehle (8) and Höst (10), to the effect that perhaps only a part of the uric acid has its origin in the alimentary cells, obviates this difficulty. Such a suggestion, however, does not afford an explanation of the effect of amino-acids, which require no digestion, upon uric acid elimination. Lewis, Dunn, and Doisy (17) have shown that glycocoll, alanine, and other amino-acids increase the hourly output of uric acid during fasting as much as do proteins. In our own experiments described in the succeeding paper, the protocols show that even though the subjects lived upon weighed diets, necessitating the daily expenditure of the same amount of physiological labor in the process of digestion, the uric acid output for the individual days of the periods was quite variable.

Smetánka (6), who in the main adheres to the Mareš theory, was forced to modify it in view of results obtained by him in experiments somewhat similar in nature to those of Lewis, Dunn, and Doisy. Having observed that the ingestion of honey, a food which like amino-acids requires practically no digestion, causes a marked increase in the output of uric acid, this investigator suggested that in addition to digestive work, the activity involved in glycogenesis may be responsible for a part of the endogenous uric acid. As far as the writer is aware, this is the only suggestion in the literature which specifically attributes uric acid formation in part to the process of food storage. While the theory is
interesting, and perhaps comes nearer explaining the experimental facts than does the original Mareš conception, still it is open to the same criticism as regards the action of amino-acids. If the increased output of uric acid following the ingestion of honey is due to the increased glycogenesis, certainly some other factor must be responsible for the action of glycocoll, alanine, and other compounds which cannot form appreciable quantities of this polysaccharide.

In connection with Smetánka's observation concerning the effect of honey, the investigations of Graham and Poulton (12) and of Umeda (11) are of interest. These authors believe that part of the endogenous uric acid may arise through synthesis from carbohydrates. They observed that carbohydrate-rich fat-poor diets cause a greater excretion of uric acid than do fat-rich carbohydrate-poor diets, even though the protein content and calorific value of the food are maintained constant. Umeda suggests that uric acid may arise from a condensation of urea with an intermediary product of carbohydrate metabolism, perhaps lactic acid. As evidence for a synthesis of purines from carbohydrates, Graham and Poulton point to the observation of Knoop and Windaus (18) that when glucose is exposed \textit{in vitro} to the action of sunlight and the strongly dissociated compound, Zn(OH)$_2$.4NH$_3$, methyl glyoxal and 5-methyl-imidazole are formed. As interesting as these suggestions are, there exists at the present time no experimental evidence \textit{in vivo} which justifies the belief that carbohydrates are transformed into purines in the animal organism. The observations of Ackroyd and Hopkins (15) which are discussed below indicate that in the rat, at least, purine synthesis from carbohydrate, if it occurs at all, is not quantitatively sufficient to meet the demands of the growing organism for these nuclear constituents.

One of the most important studies of endogenous purine metabolism of recent years is the paper of Ackroyd and Hopkins (15) alluded to above. These authors found that when young rats were supplied diets deprived of arginine and histidine, but adequate in every other respect to meet the demands of growth, growth ceased and the elimination of allantoin decreased 40 to 50 per cent. When either arginine or histidine was present in the diet, there was no loss of weight, and in some cases growth oc-
curred. The decrease in allantoin excretion was likewise much less than when both diamino-acids were absent from the food. No fall in allantoin elimination occurred when tryptophane was removed from the ration, or as a result of the absence of a vitamin supply, though nutritional failure in these cases was even greater than when arginine and histidine were withheld. Despite the difficulties which are obviously associated with metabolic studies involving quantitative urine analyses in small animals, the care with which the experiments of Ackroyd and Hopkins are controlled, and the uniformity of their results, justify, in our opinion, their conclusions that arginine and histidine are the most readily available raw materials for purine anabolism in the body. Apparently either of these amino-acids may serve as the substrate for purine formation.

A similar conclusion as to the origin of purines in the diamino-acids was recently arrived at by Harding and Young (16). According to these investigators, the feeding of placenta, which has a high content of arginine, causes a much greater increase in the output of uric acid and allantoin in young dogs than does the ingestion of an equal quantity of muscle protein. Inasmuch as the diets of their animals were not purine-free, the data of Harding and Young are not as convincing as those of Ackroyd and Hopkins.

On the contrary, Abderhalden and Einbeck (19), Abderhalden, Einbeck, and Schmid (20), and Lewis and Doisy (9) have been unable to show any relationship between the arginine and histidine content of the diet and the uric acid or allantoin output in the urine. Lewis and Doisy compared the effects of diets high and low in arginine and histidine upon the uric acid output in man. Abderhalden and Einbeck studied the effects of adding histidine to the diet upon the allantoin excretion in the dog. In the later experiment of Abderhalden and his coworkers (20), histidine hydrochloride was given in 10 gm. doses to a fasting animal. Neither of the experiments yielded any evidence for an origin of purines in the diamino-acids. We believe the procedures made use of by these investigators were not suitable for studying the relation of amino-acids to purine syntheses. In the experiments of Lewis and Doisy (9), it is quite possible that the "low" histidine-arginine diets contained adequate amounts of purine pre-
cursors to support the normal anabolism. Calculation from the authors' data shows that the "low" diets contained 3.5 to 4.0 gm. of arginine and histidine in each day's ration. If such amounts are adequate (we have no information as to the quantities of diamino-acids required by adult men), one would hardly expect that a more abundant supply would result in an exaggerated purine synthesis, and an increased uric acid elimination. We shall return to this proposition later.

Concerning the experiments of Abderhalden, the question is properly raised by Ackroyd and Hopkins (15) as to whether an abnormal condition like fasting affords the best opportunity for investigating the fate of an amino-acid. They believe¹ that the

"... synthesis of such essential tissue constituents as the purines continues during starvation, at the expense—as we are entitled to believe—of protein materials liberated by autolysis of the less essential organs. When however an excess of a single amino-acid enters the circulation of a starving animal in a single isolated dose it may well almost completely escape such special utilization. It appears suddenly in excess of current needs, and, because the processes of deamination and direct oxidation are always in action, it will almost certainly survive for but a short period as available material for synthesis."

In contrast to the methods of Abderhalden and Lewis and their coworkers, Ackroyd and Hopkins compared the effects of diets free from arginine and histidine, with diets containing adequate amounts of the diamino-acids. The importance of this procedure is emphasized by them as follows:²

"When an animal is in a state of full nutrition it does not follow that such a process as the synthesis of the purine ring would necessarily be much accelerated or increased by mere increase in the supply of its raw material."

And again,²

"An individual amino-acid fed in excess of the immediate current needs of the tissues, as when it is added to an already efficient dietary, will almost certainly be rapidly broken down on more direct lines, even if it be a normal precursor of the purine (or other) synthesis in the body."

¹ Ackroyd and Hopkins (15), pp. 552 and 553.
² Ackroyd and Hopkins (15), p. 552.
As important as the investigations of Ackroyd and Hopkins appear to us, we do not believe that they, or other studies of their kind, have an immediate bearing upon the problem of the variations in endogenous uric acid elimination incident to alterations in the kind and amount of purine-free food, when the amino-acids in question are included in the diet. Even if it be admitted, as we are prepared to do, that tissue purines have their ultimate origin in arginine and histidine, this fact, in our opinion, does not warrant making the assumption that the extent of purine synthesis is proportional to the arginine-histidine supply. On the contrary, it seems reasonable to suppose that the anabolism of any tissue component is limited quantitatively to the needs of the organism for that particular ingredient. As soon as a diet contains sufficient precursors of any given anabolic product, synthesis of that product at the optimum rate probably occurs. It seems unlikely that the optimum would be exceeded however great a redundance of the precursors in question were provided. We believe that this view is entirely in accord with the statements of Ackroyd and Hopkins quoted above, and is completely justified in the case of purine anabolism by the experiments of Abderhalden and Lewis and Doisy. If we are correct, one should no more expect to exaggerate purine anabolism by feeding excessive quantities of purine precursors, than he should anticipate being able to increase the mass of brain substance by feeding unusual amounts of the components of nervous tissue. With the exception of the purely storage forms of foods (glycogen, fats, and to a less extent, amino-acids), the components of the tissues of each species are normally synthesized and retained in remarkably uniform proportions. If conditions were otherwise, tissue composition would be largely determined by the accident of diet rather than by the expression of the inherent, hereditary tendencies and impulses of the organism. It is, therefore, rather surprising to us that Harding and Young (16) were able to note differences in purine excretion in pups on diets of placenta (high in diamino-acids) as contrasted with diets of muscle (low in diamino-acids), unless the differences were in part due to exogenous purines. On the other hand, the fact that in their experiments growing animals were used, in which the anabolic reactions are known to predominate, may have been responsible for their unique data.
In accordance with these concepts, instead of there being conflict between the data of Ackroyd and Hopkins on the one hand, and Lewis and Doisy on the other, we regard them as entirely in accord and mutually supplementary. In the experiments of the former, the decrease in allantoin excretion following the removal of arginine and histidine from the diet is the significant point, rather than the increase, which probably represented the normal purine metabolism, when the diamino-acids were supplied. After removal of arginine and histidine from the diet growth ceased because purine (and perhaps other) anabolism was no longer possible. Because of the deficient anabolism, greater physiological enconomy was exercised in catabolism, and the catabolic end-product of purines in the rat (allantoin) decreased in amount. In the experiments of Lewis and Doisy, a high arginine-histidine diet failed to induce a greater elimination of the catabolic end-product of purines in man (uric acid) than did a low arginine-histidine diet, because the latter was adequate to permit the optimum anabolism of purines. The superfluous molecules of arginine and histidine were doubtless oxidized without passing through the purine stage. In other words, the work of Ackroyd and Hopkins, to our mind, renders it very probable that the ultimate sources of tissue purines are arginine and histidine; the investigation of Lewis and Doisy indicates that purine anabolism in the adult is limited in extent to the physiological needs of the organism for purines. Neither investigation, however, permits any conclusions to be drawn as to the cause of variations in purine elimination with diets containing adequate amounts of diamino-acids. The latter problem is more likely one of purine catabolism or excretion rather than of anabolism.

In the course of the exceedingly interesting investigation of Lewis, Dunn, and Doisy (17) on the influence of diet upon the hourly elimination of uric acid, the possibility occurred to the authors that the increased uric acid excretion following the ingestion of a single dose of a protein or of an amino-acid might be due to a stimulation of the processes of excretion under the influence of the food, rather than to increased uric acid formation. They reasoned that if a single dose of an amino-acid produced its effect by bringing about the mobilization and elimination of reserve or stored purines or their precursors, the administration of a
second dose, after the effect of the first had reached its maximum, should be without further influence. Accordingly, an experiment was made in which successive doses of glycocol had been administered on the same experimental day. The figures show that entirely comparable increases in the hourly output of uric acid occurred after each dose. According to the authors the data\(^3\) "clearly demonstrate that the effects of amino-acids on uric acid excretion are not the result of stimulation of excretory processes leading to a removal of preformed uric acid from the body." While it might be questioned whether Lewis, Dunn, and Doisy were justified in assuming that the first dose of glycocol entirely removed all excess or reserve purines from the system, and whether the single experiment reported by them is sufficient to warrant their conclusion in this regard, data of another sort in the literature, when considered in connection with their work, increase the probability of their contention being well founded. Frequent estimations of uric acid in the blood of normal subjects upon widely different purine-free diets led Höst (\(^10\)) to the conclusion that diet (in the absence of purines) is without influence upon the concentration of uric acid in the blood. Despite the fact that urinary uric acid varies greatly in a given individual as a result of changes in the composition of the food, the proportion in the blood remains constant within the experimental error of the method. Inasmuch as uricolysis is not believed to occur in the human subject, and since the concentration of uric acid in normal blood is invariable under the influence of purine-free food, Höst is of the opinion\(^4\) that "the endogenous uric acid output becomes a direct expression for the uric acid formation." It must be admitted that rather large quantities of uric acid would have to be retained in the blood in order to alter appreciably the proportion present, or that reserve purines in the sense of Lewis, Dunn, and Doisy might be stored in the tissues, and hence not be manifested by blood analyses at all. Nevertheless, such evidence as we have, whether obtained from a study of the urine (Lewis, Dunn, and Doisy), or by means of blood analyses (Höst), indicates that the cause of the alterations in output of endogenous

\(^3\) Lewis, Dunn, and Doisy (17), p. 17.

\(^4\) Höst (10), p. 30.
uric acid following food consumption is not to be sought in an exaggerated excretion.

Having excluded to their own satisfaction the possibility of a stimulation in excretion being the causative factor in the increased output of uric acid following protein ingestion, Lewis, Dunn, and Doisy (17) suggest that the effect may be due to a general stimulation of all cellular metabolism by amino-acids. Each of the four amino-acids, glycocoll, alanine, glutaminic acid, and aspartic acid, as well as the closely related asparagine, caused an appreciable increase in the hourly fasting output of uric acid. The stimulation caused by the dicarboxylic amino-acids was more marked than that produced by glycocoll and alanine. On the other hand, sarcosine, a substituted amino-acid not readily catabolized by the body, and ammonium chloride and urea, were without influence. The authors emphasize the similarity of the effects produced by protein and amino-acid ingestion upon uric acid formation and heat production (specific dynamic action), and point out that the same chemical factors may be responsible for both.

We believe that there are no experiments in the literature the results of which invalidate the assumption that general stimulation of cellular catabolism, involving both the nuclear purines and the hypoxanthine of muscle tissue, by amino-acids is at least one of the important factors in endogenous purine metabolism. Particularly do the data of Smetánka (6), Taylor and Rose (7), Mendel and Stehle (8), and Höst (10) lend support to this hypothesis. In the succeeding paper we shall present the results of observations which we believe afford additional reasons for accepting this view.

BIBLIOGRAPHY.

THE INFLUENCE OF FOOD INGESTION UPON ENDOGENOUS PURINE METABOLISM. I
William C. Rose


Access the most updated version of this article at http://www.jbc.org/content/48/2/563.citation

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 0 references, 0 of which can be accessed free at http://www.jbc.org/content/48/2/563.citation.full.html#ref-list-1